

### REMARKS/ARGUMENTS

Claims 12, 15-17, 34, 40, 42, and 46 are amended as described herein below. Support for the amendments can be found throughout the specification and in the original claims. Therefore, no new matter has been added by way of claim amendment. Entry of these claim amendments into the above-referenced application is respectfully requested.

Amendments to the specification have been made at pages 2, 5, 19, 23, 29, and 37 to identify Herceptin<sup>®</sup> and Proleukin<sup>®</sup> as registered trademarks, and at pages 9, 11, 27, 30, 32, and 36 to replace the phrase “mIU/m<sup>2</sup>” with the phrase “MIU/m<sup>2</sup>.” The specification has also been amended at page 24 to correctly identify the binding characteristics of the anti-HER2 antibody fragment; support for recitation of binding to the “HER2 receptor protein” resides in the specification, for example, at page 24, lines 3-4. These amendments were made to correct for obvious typographical errors and use of registered trademark designations. No new matter has been added by way of these amendments.

Independent claims 12, 16, 17, and 42 have been amended to recite biologically active IL-2 variants that have at least 70% sequence identity with IL-2 as calculated using the ALIGN program with a PAM 120 weight residue table, a gap length penalty of 12, and a gap penalty of 4. Support for recitation of “biologically active” IL-2 variants resides, for example, at page 12, line 20, of the specification, and support for recitation of the ALIGN program with the stated parameters resides at page 15, lines 8-10, of the specification. These independent claims, as well as claims 24 and 30, have been amended to recite anti-HER antibody fragments that retain the ability of the anti-HER2 antibody to bind the HER2 receptor protein. Support for this limitation resides in the specification, for example, at page 24, lines 3-4. Responsive to the Examiner’s objection, the independent claims have also been amended to clarify that the subject is undergoing treatment for a cancer that is characterized by overexpression of the HER2 receptor protein.

Claims 20, 21, 41, 48, 49, and 50 have been amended for purposes of clarifying that the intermediate dose IL-2 pulsing comprises administering an intermediate dose of about 12.0 MIU/m<sup>2</sup> IL-2 or variant thereof in place of the therapeutically effective dose of IL-2 or variant thereof. Claims 24, 25, 30, and 31 have been amended to clarify the particular anti-HER2 antibody being administered. Support for recitation of humanized, chimeric, and human anti-HER2 antibodies resides in the specification and in the original claims, as noted further herein

below. In view of the amendments to base claims, claim 27 has been amended to recite recombinantly produced human IL-2 or variant thereof. Accordingly, claim 28 has been amended to recite a specific IL-2 variant, the des-alanyl-1, serine-125 human IL-2 mutein. Support for recitation of this mutein resides in the specification, for example at page 29, lines 6-7. No new matter is added by way of these amendments to the claims.

New claims 51-62 have been added. Claims 51, 54, 57, and 60 recite specific embodiments of the independent claims, where the subject being treated has breast cancer. New claims 52, 55, 58, and 61 recite that the anti-HER2 antibody is a humanized form of the murine antibody 4D5 or 520C9. Support for this claim resides throughout the specification and in the original claims. New claims 53, 56, 59, and 62 are directed to use of recombinantly produced human IL-2 or biologically active variant thereof. Support for these claims resides throughout the specification as noted herein above. No new matter is added by way of presentation of these new claims.

Claims 12-62 are now pending in the application. Entry of these amendments is respectfully requested. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

#### The Objections to the Specification Should Be Withdrawn

The specification is objected to because "on page 24, in lines 4-6, it teaches that a fragment of an anti-HER2 antibody will retain the ability to bind CD20." (See the March 14, 2003 Office Action, hereinafter 'Office Action', at page 3). Applicants respectfully submit that the cited passage contains an obvious typographical error. The previous sentence in the specification (at page 24, lines 3-4) states, "Fragments of the anti-HER2 antibodies are suitable for use in the methods of the invention so long as they retain the desired affinity of the full-length antibody." Because this sentence is followed by the sentence at lines 4-6 cited by the Examiner (which begins with, "Thus, a fragment of an anti-HER2 antibody will..."), proper sentence construction and common usage dictates that the properties of an anti-HER2 antibody fragment according to the present invention were to be further described. Furthermore, as described at page 24, lines 3-4, the term "anti-HER2 antibody" is defined for the purposes of the present application as "any antibody that specifically recognizes and specifically binds to the HER2 protein, preferably to the extracellular domain of the HER2 protein." Applicants have

amended the specification to correct this obvious typographical error and change the reference to "CD20B" to "HER2 receptor protein." Applicants submit that this objection is therefore obviated.

The Office Action states that the nature of the references within the specification to "the CALGB 9661 Protocol" (i.e., whether it is published or unpublished) cannot be ascertained. The sentence that carries over from page 2, line 30 to page 3, line 4, states "In another clinical trial, monotherapy with Herceptin® yielded objective responses in 5 out of 43 assessable metastatic breast cancer patients (11.6%) (as cited in "Cancer and Leukemia Group B (CALGB) 9661, A Pilot Study of Low-dose Interleukin-2 plus Recombinant Human Anti-HER2 Monoclonal Antibody in Solid Tumors"; herein incorporated by reference)." Applicants respectfully submit that this statement indicates that the cited protocol is from a clinical trial, and that this is the standard citation method for citing to a clinical trial protocol. Should the Examiner deem it necessary for Applicants to submit a copy of this protocol, a copy will be submitted at that time.

#### Objections to Claims

Claims 43-46 are objected to on the grounds that they are substantially duplicates of claims 18 and 38-40, respectively, and that "when two claims in an application ... both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim." (See the Office Action, at page 4). As the Examiner himself states, such an objection is only proper after one or more of the above claims have been allowed. Until the Examiner specifies which claims in the present application are allowable, Applicants respectfully submit that this objection is improper and should be withdrawn.

Claims 12-50 are objected to on the grounds that claims 12, 16, 17, and 42 recite the phrase "a cancer characterized by overexpression of the HER2 receptor protein in a subject," and that such a phrase "is objectionable because it is not clear that the cancer is characterized by overexpression of HER2, and not by a subject in whom HER2 is overexpressed." (See the Office Action, at page 4). Claims 12, 16, 17, and 42 have been amended to recite a "method for treating a subject for a cancer characterized by overexpression of the HER2 receptor protein." Applicants respectfully submit this amendment clarifies that it is the cancer that is characterized by overexpression of HER2, thereby obviating this objection.

The specification and claims 12-50 are objected to on the grounds that the specification and claims "teach or recite that initial IL-2 doses typically, or preferably range from about 0.5 to about 4.0 mIU/m<sup>2</sup>, while pulse doses of IL-2 are typically, preferably about 12 mIU/m<sup>2</sup>." (See the Office Action, at page 4). This objection is raised because "the Examiner firmly believes the appropriate low-dose of IL-2 more typically might range from about 0.5 to about 4.0 MIU/m<sup>2</sup>, while the appropriate pulse might more typically be about 12.0 MIU/m<sup>2</sup>, but not more than 12.0 MIU/m<sup>2</sup>." (See the Office Action, at page 4). The specification and claims have been amended accordingly to replace the term "mIU/m<sup>2</sup>" with the term "MIU/m<sup>2</sup>" to correct this obvious typographical error. Accordingly, this objection is obviated and should be withdrawn.

Claims 15, 43, 40, and 46 are objected to on the grounds that "the claims recite limitations requiring the therapeutically effective dose [sic] of anti-HER2 antibody or fragment thereof to be about 4.0 mg/m<sup>2</sup>" and that the therapeutically effective dose "may not fall within the therapeutically effective doses recited in the claims from which [these claims] depend" based upon differences in the size and mass of the subject. (See the Office Action, at page 4). Applicants have amended these claims to recite limitations requiring the therapeutically effective dose of anti-HER2 antibody or fragment thereof to be "about 4.0 mg/kg." Support for this amendment resides in the original base claims and in the specification, for example, at page 9, line 26. Accordingly, Applicants submit that this objection has therefore been obviated and should be withdrawn.

The Rejections of the Claims Under 35 U.S.C. §112, First Paragraph, Should Be Withdrawn

*Written Description*

Claims 25 and 31 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in such a way as to reasonably convey to one skilled in the art that the inventor(s) had possession of the claimed invention at the time the application was filed. The rejection is based upon the Examiner's assertion that the recitation of "human form thereof" is without proper antecedent basis. This rejection is respectfully traversed.

As an initial matter, claims 25 and 31 as amended for clarification now recite that the anti-HER2 antibody is "a humanized, chimeric, or human form of a murine antibody selected from the group consisting of 4D5 and 520C9." Furthermore, claims 24 and 30 as amended for clarification now recite an anti-HER2 antibody "selected from the group consisting of a

humanized anti-HER2 antibody, a chimeric anti-HER2 antibody, or a human anti-HER2 antibody.” Applicants respectfully submit that the specification provides sufficient written description to reasonably convey to one skilled in the art that the inventors had possession of the claimed “human form” of an anti-HER2 antibody at the time the application was filed.

The Examiner acknowledges that this issue may be resolved if Applicants point to particular disclosures in the specification that are believed to provide the necessary explicit, expressive, or implicit support for this limitation. Applicants therefore call the Examiner’s attention to the paragraph that runs from page 23, line 26, to page 24, line 2, of the specification. This passage states, in pertinent part, that “the term anti-HER2 antibodies” also encompasses “xenogeneic or modified anti-HER2 antibodies produced in a non-human mammalian host, more particularly a transgenic mouse,” and that “in such transgenic animals, competent endogenous genes for the expression of light and heavy subunits of host immunoglobulins are rendered non-functional and substituted with the analogous human immunoglobulin loci.” Furthermore, the passage states that “[t]hese transgenic animals produce *human* [emphasis added] antibodies in the substantial absence of light or heavy host immunoglobulin subunits. See, for example, U.S. Patent No. 5,939,598, herein incorporated by reference.”

Furthermore, Applicants refer the Examiner to the specification from page 24, line 7, to page 25, line 10. This passage further states that “A humanized antibody has one or more amino acid residues introduced into it from a source that is non-human ... [h]umanization can be essentially performed following the method of Winter and co-workers (Jones *et al.* (1986) *Nature* 321:522-525; Riechmann *et al.* (1988) *Nature* 332:323-327; Verhoeyen *et al.* (1988) *Science* 239:1534-1536), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a *human* [emphasis added] antibody. See, for example, U.S. Patent Nos. 5,225,539; 5,585,089; 5,693,761; 5,693,762; 5,859,205; herein incorporated by reference.” The passage goes on to state that “such ‘humanized’ antibodies may include antibodies wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically *human* [emphasis added] antibodies in which some CDR residues and possibly some framework residues are substituted by residues from analogous sites in rodent antibodies. See, for example, U.S. Patent Nos. 5,225,539; 5,585,089; 5,693,761; 5,693,762; 5,859,205.”

Furthermore, the monoclonal antibody Trastuzumab (i.e., Herceptin<sup>®</sup>) is a recombinant humanized monoclonal antibody that was well known in the art at the time of the present invention. This antibody is an IgG<sub>1</sub> kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2. See the specification at page 29, lines 13-17. U.S. Patent No. 5,772,997, which was incorporated by reference, claims and discloses a human form of the murine antibody 4D5. Finally, U.S. Patent No. 6,054,561, which was also incorporated by reference, discloses a human form of the murine antibody 520C9.

In view of the state of the art at the time of Applicants' invention, which is fully supported by the disclosure of the present invention, Applicants respectfully submit that one of skill in the art would understand that the above cited passages provide the necessary explicit, expressive, or implicit support for the limitation for a "human" anti-HER antibody recited in amended claims 24 and 30 and for the limitation for a "human form" of the murine antibodies 4D5 and 520C9 recited in amended claims 25 and 31. In view of this, the rejection of claims 25 and 31 for lack of sufficient written description should be withdrawn, and should not be applied to amended claims 24 and 30.

Claims 12-50 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in such a way as to reasonably convey to one skilled in the art that the inventor(s) had possession of the claimed invention at the time the application was filed. The rejection is based upon the Examiner's assertion that the claims are drawn to administration of interleukin-2 (IL-2) or a variant thereof but that the specification includes only a written description of one species of the genus of IL-2 variants without any teaching of how Proleukin<sup>®</sup> is representative of the genus of IL-2 variants. Under this same rejection, the Examiner also states that claims 27-31 are drawn to administration of human IL-2 or a variant thereof, while claims 28-31 are drawn to recombinant variants of IL-2 having at least 70% identity to human IL-2, and that in both cases the specification does not teach the amino acid sequence of human IL-2, features thereof to distinguish it from other sequences, or substitutions that may be made while retaining such features. Under this same rejection, the Examiner also states that claims 25 and 31 are drawn to methods comprising administering to a subject the human form of 4D5, but

that the specification does not describe a human form of 4D5. This rejection is respectfully traversed.

As an initial matter, the claimed methods of the present invention require that the IL-2 or variant thereof be administered in a therapeutically effective amount. The specification clearly states that a therapeutically effective amount of the IL-2 or variant thereof is "an amount of the anti-tumor agent that, when administered with a therapeutically effective dose or amount of the other anti-tumor agent, brings about a positive therapeutic response with respect to treatment of cancers characterized by overexpression of the HER2 receptor protein" (page 7, lines 27-30, of the specification). Further, the specification states that variants of IL-2 will retain the desired biological activity of the native IL-2 polypeptide "such that the pharmaceutical composition comprising the variant polypeptide has the same therapeutic effect as the pharmaceutical composition comprising the native polypeptide when administered to a subject. That is, the variant polypeptide will serve as a therapeutically active component in the pharmaceutical composition in a manner similar to that observed for the native polypeptide" (page 12, lines 21-27, of the specification). Thus, it is clear that the claimed variants of IL-2 have function similar to the native IL-2 polypeptide, and the claims do not read upon non-functional variant polypeptide sequences or variant polypeptide sequences that lack the ability to restore immune function when administered in accordance with the claimed treatment regimens.

In addition, the claimed methods of the invention require that the variant IL-2 has at least 70% sequence identity with the amino acid sequence for IL-2 as calculated using the ALIGN program with a PAM 120 weight residue table, a gap length penalty of 12, and a gap penalty of 4. Amended claims 27-31 recite human IL-2, and amended claim 28 recites a specific variant of human IL-2, i.e., des-alanyl-1, serine-125 human IL-2, which is the recombinant protein present in Proleukin<sup>®</sup>. Human IL-2 is also recited in new claims 53, 56, 59, and 62. Applicants respectfully submit that the specification provides sufficient written description for the invention as claimed for the following reasons.

Applicants note that, in order to satisfy the written description requirement, the application must reasonably convey to persons skilled in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him. *See Ex parte Parks*, 30 USPQ 1234, 1236-37 (B.P.A.I. 1993). The Examiner has the burden of presenting evidence or reasons why persons skilled in the art would not recognize in the specification disclosure a

description of the invention defined by the claims. *Ex parte Sorenson*, 3 USPQ2D 1462, 1463 (B.P.A.I. 1987).

The description of a claimed genus can be by structure, formula, chemical name, or physical properties. *See Ex parte Maizel*, 27 USPQ2d 1662, 1669 (B.P.A.I. 1992), *citing Amgen v. Chugai*, 927 F.2d 1200, 1206 (Fed. Cir. 1991). A genus of DNAs may therefore be described by means of a recitation of a representative number of DNAs, defined by nucleotide sequence, falling within the scope of the genus, *or* by means of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997); *see also* Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (2000). Similarly, in the present case, a genus of polypeptides may therefore be described by means of a recitation of a representative number of polypeptides, defined by amino acid sequence, falling within the scope of the genus, *or* by means of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Applicants respectfully submit that the recitation of a predictable structure based upon 70% sequence identity to IL-2 is sufficient to satisfy the written description requirement.

The recitation of at least 70% sequence identity at the amino acid level is a very predictable structure of the sequences encompassed by the claimed invention. The Examiner is reminded that the description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. 66 Fed. Reg. 1099, 1106 (2000). Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. 66 Fed. Reg. 1099, 1106 (2000). Applicants submit that the knowledge and level of skill in the art would allow a person of ordinary skill to envision the claimed invention, i.e., a polypeptide having at least 70% sequence identity to a native IL-2 polypeptide.

Applicants note that IL-2 is a well-known protein for which the structure/function relationship and role in the immune response have been studied for over twenty years and are now well documented. *See*, for example, the review entitled "Interleukin 2," from R & D

Systems, which provides further evidence of the extensive knowledge regarding IL-2 and variant IL-2 sequences that was known to those of skill in the art at the time of the present invention. This review is provided herewith as Appendix A. As noted in this review, knowledge as to the three-dimensional structure of human IL-2 was known as early as 1987, and early mutational analysis facilitated the understanding of the structure/function relationship of IL-2. The amino acid and nucleotide sequences for human IL-2, and variant IL-2 sequences, are also well known to those of skill in the art, and further disclosed in the specification, for example, at pages 12-14 and 17.

Furthermore, as disclosed in the specification at page 14, lines 1-6, the present invention specifically envisions variants derived from “[c]onservative substitutions, such as exchanging one amino acid with another having similar properties,” and that “[i]n constructing variants of the IL-2 polypeptide of interest, modifications are made such that variants continue to possess the desired activity.”

With respect to the Examiner’s assertion under this rejection that the specification does not describe a human form of 4D5, Applicants submit that for reasons noted above the specification provides sufficient written description to support this aspect of the claimed invention. See particularly U.S. Patent No. 5,772,997, which discloses and claims a human form of 4D5 and which was incorporated by reference in its entirety into the present specification.

In view of the state of the art at the time of Applicants’ invention, which is fully supported by the disclosure of the present application, Applicants respectfully submit that one of skill in the art could envision Applicants’ invention and would recognize that Applicants were in possession of the claimed members of the genus at the time the invention was made. In view of this, the rejection of the claims for lack of sufficient written description should be withdrawn.

#### *Enablement*

Claims 12-50 are rejected under 35 U.S.C. §112, first paragraph, as lacking enablement for a method for treating a subject having cancer that is characterized by overexpression of HER2. The rejection is based upon the Examiner’s assertion that one of skill in the art could not have a reasonable expectation of success in practicing the claimed invention without having the need to perform additional, undue experimentation to determine which variants of IL-2 would have efficacy for treating cancer. The Examiner cites to Skolnick *et al.* (*Trends in Biotechnology*

18: 34-39, 2000) in support of the assertion that the art of protein chemistry is highly unpredictable and that the specification discloses use of Proleukin<sup>®</sup> but no other species of the genus of IL-2 molecules to which the claims refer. The Examiner further states that it is well known to those skilled in the art at the time of the claimed invention that minor structural differences among structurally related compounds can result in substantially different biological and pharmacological activities.

Applicants contend that the Examiner's reasons of record do not establish a *prima facie* case by the mere assertion that a large number of variants could be made and that some of those variants might have unpredictable structures or functions. The speculative nature of this assertion regarding the disclosed invention is insufficient to meet the burden of proof. The burden of proof is on the Examiner to identify the variants or class of variants that are non-enabled and support this assertion with either personal knowledge or references pertaining to this invention. Until this evidence is presented, no rebuttal is required or even possible because the Examiner has not defined the portion of the invention that the Examiner believes is beyond the scope of enablement. Therefore, the rejection is traversed.

Applicants note that the M.P.E.P. states that "a specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* [emphasis added] be taken as being in compliance with the enablement requirement of 35 U.S.C. §112, unless there is reason to doubt the objective truth of the statements contained therein" M.P.E.P. §2164.04 *citing In re Marzocchi* 439 F.2d 220, 223(CCPA 1971). The Examiner has not cited any references or stated any personal knowledge that would lead one to doubt whether the claimed IL-2 molecules or variants could be made. Therefore, because the Examiner has not met the *prima facie* burden, the rejection is respectfully traversed.

To the extent that the Examiner is rejecting the claims as non-enabled because some of the variants that can be created might not have therapeutic activity, the Examiner fails to meet the required burden of proof. The Examiner does not allege that all of the variants of IL-2 will be nonfunctional or even allege with any certainty that some will be. The Examiner simply notes that some variants of IL-2 might be inoperative. The mere supposition that some variants might be nonfunctional is insufficient evidence to create a *prima facie* case of nonenablement of the claimed invention. The Examiner must demonstrate with some certainty that the variants will

necessarily be inoperative. The previously cited reference, Skolnick *et al.* (2000) only demonstrates that in proteins entirely unrelated to IL-2, mutations may (but not necessarily) result in nonfunctional proteins. Therefore, this reference merely demonstrates uncertainty within the field of protein chemistry; it does not demonstrate that the invention as disclosed is or will likely be inoperative. Without producing any evidence that the disclosed invention will be nonfunctional in any of the embodiments, the Examiner fails to meet the burden of proof for a *prima facie* case, and thus the rejection should be withdrawn.

Additionally, to the extent that the Examiner is rejecting the claims for lack of an enabling disclosure because the variants will need to be screened as therapeutic agents because a variant may have "unpredictable structure and function," the Federal Circuit has expressly stated that experimentation is allowed with regard to multiple embodiments of a disclosed invention as long as the experimentation is not undue. *In re Wands*, 858 F.2d 731, 734 (Fed. Cir. 1988). Applicants respectfully point out that it is the burden of the Examiner to show why one skilled in the art would consider the amount of experimentation undue. M.P.E.P. §2164.04. The Examiner has merely pointed out that some testing will need to be done, not that this testing is undue. Because a need for further experimentation alone is insufficient to create a *prima facie* case without evidence that the amount of testing is undue, the Examiner fails to make a *prima facie* case, and the rejection should be withdrawn.

Applicants stress that when evaluating the quantity of experimentation required, the court looks to the amount of experimentation required to practice a single embodiment of the invention, rather than the amount required to practice every embodiment of the invention. For example, in *Wands*, the claims at issue were drawn to immunoassay methods using any monoclonal antibody having a binding affinity for HbsAg of at least  $10^{-9}$  M. *In re Wands*, 858 F.2d 731, 734 (Fed. Cir. 1988). The USPTO had taken the position that the claim was not enabled, as it would take undue experimentation to make the monoclonal antibodies required for the assay. *Id.* at 736. The Federal Circuit reversed, and held that the claims were enabled, as the amount of experimentation required to isolate monoclonal antibodies and screen for those having the correct affinity was not undue, even though the success rate was less than 3%. *Id.* at 740. Clearly, the Federal Circuit did not contemplate that every antibody useful in the claimed methods must be identified or even be functional. Rather, the court considered the amount of

experimentation required to identify one or a few monoclonal antibodies having the required affinity.

In the instant case, the quantity of experimentation required to practice the invention amounts to two steps, generating an IL-2 molecule or variant, and assaying the obtained protein for therapeutic activity. Those of skill in the art often carry out experiments such as mutagenesis analysis of the molecule of interest. For example, the technique of "shuffling" commonly used in the art involves screening entire libraries of recombinant polynucleotides to determine whether the generated recombined polynucleotides encode a polypeptide that retains a desired activity. Because those of skill in the art would not consider the amount of experimentation to make and determine whether a given polypeptide fragment or variant fell within these claims to be undue, this rejection is traversed.

Even in the event that the Office Action would have made a *prima facie* case, the claims and the specification provide adequate support for enablement of the recited variants, in terms of both definitive structural and functional properties. As stated previously, the specification states that variants of IL-2 will retain the desired biological activity of the native IL-2 polypeptide "such that the pharmaceutical composition comprising the variant polypeptide has the same therapeutic effect as the pharmaceutical composition comprising the native polypeptide when administered to a subject. That is, the variant polypeptide will serve as a therapeutically active component in the pharmaceutical composition in a manner similar to that observed for the native polypeptide" (page 12, lines 21-27, of the specification). Thus, it is clear that the claimed variants of IL-2 have function similar to the native IL-2 polypeptide, and the claims do not read upon non-functional variant polypeptide sequences or variant polypeptide sequences that lack the ability to restore immune function when administered in accordance with the claimed treatment regimens.

Furthermore, as described previously, Applicants note that IL-2 is a well-known protein for which the structure/function relationship and role in the immune response have been studied for over twenty years and are now well documented. See, for example, the review entitled "Interleukin 2," from R & D Systems, which provides further evidence of the extensive knowledge regarding IL-2 and variant IL-2 sequences that was known to those of skill in the art at the time of the present invention. This review is provided herewith as Appendix A. Knowledge as to the three-dimensional structure of human IL-2 was known as early as 1987, and

early mutational analysis facilitated the understanding of the structure/function relationship of IL-2. The nucleotide and amino acid sequences for human IL-2, and variant IL-2 sequences, are well known to those of skill in the art, and further disclosed in the specification, for example, at pages 12-14 and 17.

In addition, all claims drawn to variant IL-2 sequences require that the IL-2 variant be at least 70% identical to the IL-2 sequence, where sequence identity is determined using a specific algorithm, i.e. the ALIGN program with a PAM 120 weight residue table, a gap length penalty of 12, and a gap penalty of 4. Methods for producing variant IL-2 polypeptides are disclosed in the specification. Applicants again point to the specification at page 14, lines 1-6, in which the present invention is specifically described in terms of variants being derived from “[c]onservative substitutions, such as exchanging one amino acid with another having similar properties,” and that “[i]n constructing variants of the IL-2 polypeptide of interest, modifications are made such that variants continue to possess the desired activity.” Furthermore, variant polypeptides having at least 70% sequence identity with their respective native-sequence polypeptide are defined in the specification at page 14, lines 11-14. Sequence identity is defined at page 14, lines 17-21. Thus, the specification describes methods for producing variant polypeptides and further provides examples of variant polypeptides. See page 13, line 21, through line 10 of page 14. The specification provides several routine bioassays for testing biological activity of IL-2 activity including the HT-2 cell proliferation assay. See, for example, at page 12, line 27 to page 13, line 5.

Given this disclosure, one of skill in the art could readily make polypeptide variants of IL-2 and test for their biological activity without undue experimentation. As noted above, methods for making polypeptide variants of IL-2 and determining biological activity of these variants are well known in the art, and specific examples are disclosed in the specification. In light of the above statements, Applicants respectfully submit that the claimed methods are fully enabled by the specification. Accordingly, this rejection should be withdrawn.

Claims 12-50 are further rejected on the grounds that they encompass methods comprising administering to a subject a fragment of an anti-HER2 antibody, but that the claims are not limited to those antibodies that retain binding specificity of the full-length antibody. Independent claims 12, 16, 17, and 42 have been amended to incorporate the limitation that anti-

HER2 antibody fragments must retain the ability of the full-length antibody to bind HER2. Therefore, Applicants maintain that this rejection has been obviated, and therefore should be withdrawn.

Claims 12-50 are further rejected on the grounds that the claims encompass methods comprising administering to a subject an antibody that binds a non-extracellular domain of HER2, but that Applicants fail to disclose antibodies that bind to the intracellular domain of HER2 and which have been found to be therapeutically useful, and that those anti-HER antibodies that are disclosed bind to the extracellular domain. Applicants respectfully submit that the Examiner's reasons of record do not establish a *prima facie* case by the mere assertion that antibodies that bind to the intracellular domain might be found not to be therapeutically useful. The speculative nature of this assertion regarding the disclosed invention is insufficient to meet the burden of proof because the Examiner has not cited any references or stated any personal knowledge that would lead one to doubt whether antibodies that bind to the intracellular domain would be therapeutically useful. See M.P.E.P. §2164.04, *citing In re Marzocchi* 439 F.2d 220, 223 (CCPA 1971). Furthermore, Applicants respectfully note that it is improper to limit the scope of an Applicant's claimed invention to that which is disclosed in working examples. See *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973), where the court held "we do not regard section 112, first paragraph, as requiring a specific example of everything *within the scope* of a broad claim. . . . What the Patent Office is here apparently attempting is to limit all claims to the specific examples, notwithstanding the clear disclosure of a broader invention. This it may not do." Therefore, for the reasons provided above, the rejection is respectfully traversed.

The Office Action provides several additional lines of reasoning for rejecting claims 12-50, which Applicants will address together. First, claims 12-50 are further rejected on the grounds that some antibodies that bind to HER2 have been shown to promote tumor growth, citing Stancovski *et al.* (*PNAS USA* 88:8691-8695, 1991) and Lewis *et al.* (*Cancer Immunology & Immunotherapy* 37: 255-262, 1993), and that therefore teaching the making of anti-HER2 antibodies is insufficient to enable a skilled artisan to make an anti-HER2 antibody that is capable of inhibiting the growth of tumor cells upon administration to a subject. Second, claims

12-50 are also rejected on the grounds that the claims are drawn to methods for treating cancer but the specification discloses only patients having breast cancer as responding positively to the claimed treatment. In support of this rejection, the Examiner cites Lewis *et al.*, for example, as teaching that mouse monoclonal antibody 4D5 does not affect proliferation of gastric and colon cancer cells even though these cells express an amount of HER2 that is reportedly equivalent to the amount expressed by breast cancer cells that are responsive to the claimed treatment. Third, on pages 13 and 14 of the Office Action, claims 13-15, 32-40, and 44-46 are rejected on the grounds that the specification does not provide guidance as to when certain embodiments should or should not be practiced since the specification does not explicitly teach the most appropriate dose that should be selected. The Examiner states that one of skill in the art would not have a reasonable expectation of success for practicing each of the claimed methods because “at least a few of the claimed methods could not be used to efficaciously treat the patient at hand.”

As an initial matter, Applicants respectfully note that the M.P.E.P. states that “the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art.” M.P.E.P. §2164.08(b), citing *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984). Furthermore, “the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.” M.P.E.P. §2164.08(b), citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom.; Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985); *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

In order to teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation, “not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted.” M.P.E.P. §2164.08, citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991). In addition, “all that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a ‘reasonable correlation’ to the scope of the claims.” M.P.E.P. §2164.08, citing *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970).

As demonstrated by Stancovski *et al.* (1991) and Lewis *et al.* (1993), cited by the Examiner, methods for determining whether an anti-HER2 antibody is capable of inhibiting the growth of tumor cells, as well as methods for determining whether certain monoclonal anti-HER2 antibodies affect the proliferation of different types of cancer cells, are well known in the art. The Examiner's own citation of references demonstrates that the methods for screening suitable anti-HER2 antibodies disclosed therein were well known to one skilled in the art at the time of the invention, and therefore would not require undue experimentation. Applicants therefore submit that the rejections of claims 12-50 on the grounds that some antibodies that bind to HER2 have been shown to promote tumor growth and that the claims are broadly drawn to methods for treating cancer while the specification only discloses working examples with breast cancer patients are not suitable grounds for establishing undue experimentation to practice the claimed invention. Accordingly, this aspect of the enablement rejection should be withdrawn.

With respect to the argument that the specification does not explicitly teach the most appropriate dose that should be selected, Applicants have identified the dosage range within which the compounds can be administered to achieve an efficacy for our disclosed population of patients. Clinical trial protocols such as the CALGB 9661 Protocol cited throughout the specification (e.g., in the sentence that carries over from page 2, line 30 to page 3, line 4) typically include dose escalation studies as part of the routine screening of drug dosages within a given therapeutic range. It is therefore within the skill of one in the art to identify the particular dose that would be selected for a given patient or patient population, as this type of screening falls within the type of routine testing that is known to one of skill in the art and would not be considered undue experimentation. Applicants therefore submit that this aspect of the enablement rejection should be withdrawn.

The Office Action further contends that the disclosure is not sufficient to enable the skilled artisan to make a non-recombinant or engineered antibody with a reasonable expectation of success without undue experimentation. This argument is proffered on the grounds that the Examiner infers that Applicants' invention is based upon a single mechanism whereby IL-2 enhances toxicity of at least some effector cells capable of mediating antibody-dependent cell cytotoxicity (ADCC) in the presence of Herceptin<sup>®</sup>, and further infers that any greater

effectiveness of the combination of Herceptin<sup>®</sup> and Proleukin<sup>®</sup> would depend on the ability of the antibody to mediate ADCC. See the Office Action at page 12.

Applicants respectfully note that “[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works.” *Newman v. Quigg*, 877 F.2d 1575, 1581 (Fed. Cir. 1989); see also *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570 (Fed. Cir. 1983) (“[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests.”). In the present case, Applicants’ only reference to ADCC is contained in a single paragraph in the specification on page 28, lines 5 to 17, that states in pertinent part:

Natural killer cells expanded *in vivo* with low-dose IL-2 also commonly express Fc-gamma receptors and participate in antibody-dependent cellular cytotoxicity (ADCC). In principle, antibodies capable of binding both tumor targets (Fab) and [peripheral blood mononuclear cells] (Fc) could help deliver effector cells to tumor sites, as well as augment cytotoxicity through ADCC ... Humanized anti-p185HER2 participates in ADCC with [peripheral blood mononuclear cells] derived from patients treated with subcutaneous low-dose IL-2 (see reference 10 of the CALGB 9661 Protocol).

These statements are merely descriptions of physiological effects that may or may not have translated into a therapeutic response. Experiments as disclosed in the specification confirmed an effect for concurrent therapy with IL-2 and monoclonal antibodies targeting the HER2 receptor protein to treat cancers characterized by overexpression of the HER2 receptor protein, but this effect was not tied solely to the mediation of ADCC or any other specific mechanism. The attempt by the Examiner to reject claims to monoclonal antibodies targeting the HER2 receptor protein based upon their putative ability to conform to a specific mechanism of action that is neither espoused by the Applicants nor required by law is erroneous. For these reasons, Applicants respectfully submit that these rejections should be withdrawn.

Claims 24, 25, 30 and 31 are further rejected and also objected to on the grounds that the specification does not provide evidence that the claimed biological materials are: 1) known and readily available to the public; 2) reproducible from a written description (e.g., sequenced); or 3) deposited. This rejection and objection is based upon the Examiner’s assertion at page 14 of the

Office Action that “it is unclear if cell lines that produce an antibody having the exact structural and chemical identity of the monoclonal antibodies to which the claims refer are known and publicly available or can be reproducibly isolated without undue experimentation.”

Applicants note that the M.P.E.P. states that “Applicant may show that a deposit is not necessary even though specific biological materials are required to practice the invention if those biological materials can be made or isolated without undue experimentation.” M.P.E.P § 2404.02. Furthermore, “No deposit is required ... where the required biological materials can be obtained from publicly available material with only routine experimentation and a reliable screening test.” M.P.E.P § 2404.02, citing *Tabuchi v. Nubel*, 559 F.2d 1183 (CCPA 1977) and *Ex Parte Hata*, 6 USPQ 2d 1652 (Bd Pat. App. & Int. 1987). Applicants direct the Examiner to the specification on page 22, lines 5 to 7, which states in pertinent part, “The monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler *et al.* (1975) *Nature* 256:495.” Applicants respectfully submit that, even if this were the sole methodology provided for obtaining monoclonal antibodies in accordance with the present invention, this disclosure would allow one of skill to obtain these biological materials from publicly available material with only routine experimentation and a reliable screening test.

However, the above-cited passage is part of a larger section that runs from line 2 to line 10 of page 22. From lines 2 to 5, the passage states, “the modifier ‘monoclonal’ indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method.” On lines 5 to 10 the passage continues, “The monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler *et al.* (1975) *Nature* 256:495, or may be made by recombinant DNA methods (see, *e.g.*, U.S. Patent No. 4,816,567). The “monoclonal antibodies” may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.* (1991) *Nature* 352:624-628 and Marks *et al.* (1991) *J. Mol. Biol.* 222:581-597, for example.” Furthermore, the hybridoma cell line that produces the murine antibody 4D5 is deposited as ATCC CRL 10463 and the hybridoma cell line that produces the murine antibody 520C9 is deposited as ATCC No. HB8696; see U.S. Patent Nos. 5,677,171 and 6,054,561, respectively, the contents of which were

incorporated by reference into the present specification. Each of these patents discloses monoclonal antibodies having the binding properties of these respective murine antibodies.

Applicants submit that these references are sufficient to direct one of skill in the art to multiple methods for producing monoclonal antibodies according to the present invention, all of which would allow one of skill to obtain these biological materials from publicly available material with only routine experimentation and a reliable screening test. For the reasons stated above, Applicants therefore submit that the rejections of claims 24, 25, 30, and 31 should be withdrawn.

#### The Rejections of the Claims Under 35 U.S.C. §102(b) Should Be Withdrawn

Claims 12-19, 24, 26-28, 30, 32-40, and 42-47 are rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent Nos. 4,863,726 (hereinafter the '726 patent) and 4,894,227 (hereinafter the '227 patent). This rejection is respectfully traversed.

As detailed in the M.P.E.P., "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. §2131, citing *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The M.P.E.P. also states that "the identical invention must be shown in as complete detail as is contained in the ... claim." M.P.E.P. §2131, citing *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

As admitted by the Examiner on page 17 of the Office Action, the '726 patent and the '227 patent "do not explicitly teach that a therapeutically effective dose of IL-2 is [in] the range of about 0.5 to about 4.0 mIU/m<sup>2</sup> or that a therapeutically effective dose of the antibody is in the range of about 1.0 to about 10.0 mg/kg." Because neither the '726 patent nor the '227 patent contain each and every element as set forth in the rejected claims, either expressly or inherently, the Examiner has not met the *prima facie* burden for a rejection under 35 U.S.C. §102(b) and these rejections should be withdrawn.

#### The Rejections of the Claims Under 35 U.S.C. §103(a) Should Be Withdrawn

Along with the rejections of claims 12-19, 24, 26-28, 30, 32-40, and 42-47 under 35 U.S.C. §102 as described above, these claims are rejected in the alternative under 35 U.S.C. §103 as obvious over the '726 patent or the '227 patent. These rejections are made on the grounds that

one of skill in the art could “extrapolate” from the methods described in the ‘726 patent or the ‘227 patent to arrive at the method of the present invention. (See page 18 of the Office Action). This rejection is respectfully traversed.

As an initial matter, Applicants respectfully note that one can scientifically “extrapolate” in any number of different directions from a given disclosure in a prior art reference. There is no guidance whatsoever in the ‘726 or ‘227 patents to “extrapolate” the information disclosed in these two references in the particular direction that led to Applicants’ avenue of inquiry that resulted in the present invention. Furthermore, there is no legal basis for rejecting an application on grounds of “extrapolation.” This is clearly an instance where the Examiner has used impermissible hindsight reasoning. On this basis alone, the rejection should be withdrawn.

To establish a *prima facie* case of obviousness: 1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference(s) must teach or suggest all the claim limitations. MPEP §2143, citing *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). It is Applicants’ contention that a *prima facie* case of obviousness has not been established for the rejection set forth above.

As described above in response to the rejections of these claims under 35 U.S.C. §102(b), the Examiner admits on page 17 of the Office Action that the ‘726 patent and the ‘227 patent “do not explicitly teach that a therapeutically effective dose of IL-2 is [in] the range of about 0.5 to about 4.0 mIU/m<sup>2</sup> or that a therapeutically effective dose of the antibody is in the range of about 1.0 to about 10.0 mg/kg.” Because neither the ‘726 patent nor the ‘227 patent teach or suggest all the claim limitations, the Examiner has not met the *prima facie* burden for a rejection under 35 U.S.C. §103(a), and this rejection should be withdrawn.

Claims 12-50 are further rejected under 35 U.S.C. §103(a) as being unpatentable over either the ‘726 patent or the ‘227 patent “in view of Hank *et al.* (*Cancer Research* 50:5234-5239, 1990) and Keler *et al.* (*Cancer Research* 57:4008-4014, 1997), or Silwowski *et al.* (*Seminars in Oncology* 26:60-70, 1999) and Lewis *et al.* (*Cancer Immunology & Immunotherapy* 46:318-326, 1998), and further in view of Meropol *et al.* (*Cancer Immunology & Immunotherapy* 46:318-326, 1998).” Because the Examiner does not particularly point to specific combinations of references as applied to subsets of claims, and further describes his bases for *prima facie* obviousness

rejections on page 20 of the Office Action in one continuous paragraph, Applicants are left with the interpretation that the Examiner is attempting to point to a combination of all of the above references with either the '726 patent or the '227 patent for rejection of claims 12-50. This rejection is respectfully traversed.

As stated on page 18 of the Office Action, "neither '726 nor '227 disclose that the antibody can be a recombinant antibody, such as a humanized antibody, or a chimeric antibody that comprises at least one human constant region." Further, the Office Action states that "neither '726 nor '227 explicitly teach the anti-HER2 antibody can be the mouse monoclonal antibody 4D5 or a recombinant version thereof" (page 18 of the Office Action). Also, page 18 of the Office Action states that "neither '726 nor '227 teach that the treatment regimen can or should comprise intermediate-dose IL-2 pulsing."

Finally, as noted above and admitted by the Examiner on page 17 of the Office Action, the '726 patent and the '227 patent "do not explicitly teach that a therapeutically effective dose of IL-2 is [in] the range of about 0.5 to about 4.0 mIU/m<sup>2</sup> or that a therapeutically effective dose of the antibody is in the range of about 1.0 to about 10.0 mg/kg." In fact, the '227 patent suggests, and the '726 patent claims, an IL-2 dosage range of 3-3.75 to 7.5. x 10<sup>6</sup> U/kg of host weight, which is to be administered in combination with an immunotoxin in an amount of 25 to 500 µg/kg of host weight. For a 70 kg human, this is equivalent to 210-262.5 to 525 MIU IL-2, which is to be administered in combination with 0.025 to 0.5 mg/kg of the immunotoxin. The average person is about 1.7 m<sup>2</sup>, thus the presently claimed IL-2 doses (about 0.5 MIU/m<sup>2</sup> to about 4.0 MIU/m<sup>2</sup>) are equivalent to about 0.85 MIU to about 6.8 MIU. Thus, when presented in equivalent units, the '227 and '726 patents teach combination therapy with an IL-2 dose that is at least about *31-fold higher* than the highest dose in the low IL-2 dosing range claimed in the present invention. Furthermore, the much higher IL-2 dose suggested in these two cited patents is combined with an immunotoxin dose that, in its highest value (i.e., 0.5 mg/kg immunotoxin, is only half that of the *lowest* anti-HER2 antibody dose (i.e., 1.0 mg/kg anti-HER2 antibody) suggested and claimed in the present invention. Applicants respectfully submit that the dosing regimen and doses taught by these two cited patents teach away from the IL-2/antibody dosing ranges of the presently claimed invention, and also fail to provide the requisite motivation or guidance to arrive at Applicants' claimed invention.

In order to provide support for those limitations of the present invention that are not present in the '726 patent or the '227 patent, the Examiner points to Hank *et al.*, Keler *et al.*, Silwowski *et al.*, Lewis *et al.*, and Meropol *et al.* Applicants respectfully note that the Federal Circuit recently re-emphasized the importance of motivation to combine references, stating:

When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. *See, e.g., McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001) ("the central question is whether there is reason to combine [the] references," a question of fact drawing on the Graham factors).

"The factual inquiry whether to combine references must be thorough and searching." *Id.* It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding'") (quoting *C.R. Bard, Inc., v. M3 Systems, Inc.*, 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998)).

It is Applicants' contention that either the requisite motivation to combine the teachings of the cited references is lacking or, where the motivation to combine may be present, the combination of references fails to teach all of the limitations of the presently claimed invention.

Hank *et al.* suggests that combining IL-2 with a monoclonal antibody (mAB) in clinical therapy may lead to a wider range of tumor types being responsive to immunotherapy and may enhance the efficacy of therapy by specifically targeting activated effector cells to tumor cells recognized by the mAB. The suggestion is based on ADCC-mediated cytotoxicity assays using isolated peripheral blood monocytes obtained from cancer patients that had received prior IL-2 therapy. The isolated PBM were assayed using a <sup>51</sup>Cr-release assay in standard medium, medium supplemented with IL-2 or mAB, or in a combination of IL-2 or mAB. However, this reference fails to teach the combination of IL-2/anti-HER2 antibody doses recited in the pending claims. These dosing ranges are also not taught or suggested by the '726 patent or the '227

patent. A mere suggestion that IL-2 and mAB may be beneficial in the treatment of cancer without more cannot properly serve as the basis of an obviousness rejection.

Keler *et al.* teaches a bispecific antibody (MDX-H210) that includes the monoclonal antibody 520C9 chemically linked to Fab' fragments from a monoclonal antibody that binds the human IgG Fc receptor FcγRI. The Examiner states on page 19 of the Office Action that Keler *et al.* "suggest the in vivo cytotoxic potential of MDX-H210 may be enhanced by combination therapy with cytokines." Applicants respectfully submit that one of skill in the art would not be motivated to combine Keler *et al.* with either the '726 patent or the '227 patent. Keler *et al.* does not deal with administration of the mAB 520C9, but a bispecific antibody that couples 520C9 with another mAB fragment that binds another receptor. It is unclear from the data presented in Keler *et al.* that administration of 520C9 would be expected to provide the same results as the bispecific antibody MDX-H210. The passage from Keler *et al.* that runs from column 2 of page 4010 to column 1 of page 4011 states, "To exclusively measure bispecific antibody binding activity, either antimurine IgG-PE or antihuman IgG-FITC directed to the nonbinding arm of MDX-H210 was used for detection. Therefore, binding of the murine 520C9 F(ab')<sub>2</sub> to HER2/*neu* expressed on SK-BR-3 cells ... was not detected." Thus, even if one of skill in the art would be led by Keler *et al.* to expect that, as the Examiner states, "the in vivo cytotoxic potential of MDX-H210 may be enhanced by combination therapy with cytokines," it is unclear from the results disclosed in the Keler *et al.* reference whether the "cytotoxic potential" of MDX-H210 is due to 520C9 alone, the mAB that binds FcγRI alone, or some synergistic effect from the combination of the two. For these reasons, Applicants respectfully submit that there is no motivation to combine Keler *et al.* with either the '726 patent or the '227 patent.

Furthermore, even if there were a motivation to combine the teachings of Keler *et al.* with the teachings of the '726 patent and the '227 patent, alone or with the Hanks *et al.* reference, one would still not arrive at Applicants' claimed invention. The Keler *et al.* reference also fails to teach or suggest the claimed combination of IL-2/anti-HER2 antibody dosing ranges recited in the pending claims. These claim limitations are not taught by Hanks *et al.*, or either of these two cited patents.

Silwowski *et al.* and Lewis *et al.* are directed to specific disclosures regarding the efficacy of chimeric and humanized versions of the anti-HER2 murine 4D5 monoclonal antibody in ADCC assays and murine xenograft models. Even if the teachings of these references are

combined with the teachings of Hank *et al.*, Keler *et al.*, and the guidance as to IL-2 dosing provided in the '726 patent and the '227 patent, one would not arrive at Applicants' claimed invention. Rather, the doses of IL-2 to be administered would fall within the claimed range taught by the '726 patent and the '227 patent, as there is no suggestion in these patents to dose IL-2 within the range recited in the pending claims, and the cited references do not provide the motivation to modify the IL-2 dosing range taught by these two cited patents.

Meropol *et al.* teach intermediate dose pulsing with IL-2 in patients with advanced malignancy. Though Meropol *et al.* suggest such therapy with monoclonal antibodies, such a suggestion is an invitation to experiment; it does not provide the guidance as to how to combine the teachings of the cited references and/or how to modify the cited references, to arrive at the protocols recited in the presently claimed invention.

Furthermore, the combination of Hank *et al.*, Keler *et al.*, Silwowski *et al.*, Lewis *et al.*, or Meropol *et al.* with the '726 patent or the '227 patent is based upon impermissible hindsight reasoning. Unless the Examiner shows that at the time the invention was made there was something more than a mere suggestion of success based upon the cited references, obviousness has not been demonstrated.

The Examiner argues that these references suggest that it would have been *prima facie* obvious to treat breast cancer characterized by overexpression of HER2 by concurrently administering to the subject a therapeutically effective combination of recombinant IL-2 and an anti-HER2 antibody, namely a chimeric or humanized recombinant form of the mouse monoclonal antibody 4D5, or alternatively of the mouse monoclonal antibody 520C9. The Examiner also states that it would be *prima facie obvious* to administer to the subject a therapeutically effective dose in the range of about 0.5 to about 4.0 mIU/m<sup>2</sup> and a therapeutically effective dose of the antibody in the range of about 1.0 to about 10.0 mg/kg. The Office Action basis this latter point on the fact that clinical trials would reveal the "most efficacious regimens of treatment for select individuals characterized by a number of criteria, including the predetermined level of acceptable toxicity, the effectiveness, the type and stage of the cancer, etc." (Office Action at page 20, first full paragraph).

However, the only guidance as to appropriate IL-2 doses *for combination therapy* with IL-2 and an immunotoxin such as the 520C9 antibody fall well outside the dosing range recited in the claimed invention. Therefore, Applicants contend that the prior art either teaches a

specific combination of IL-2/antibody dosing ranges that teaches away from the presently claimed invention, or generically suggests treatment of cancer with a combination of IL-2 and monoclonal antibody that targets the cancer cells. The teachings of the latter represent an invitation to experiment; yet an invitation to experiment is not sufficient grounds to reject an invention as obvious.

Judge Rich explains in *In re Tomlinson* : “[t]here is usually an element of ‘obviousness to try’ in any research endeavor, that it is not undertaken with complete blindness, but with some semblance of a chance of success, and that patentability determinations [of obviousness] based on that as a test would not only be contrary to statute but result in a marked deterioration of the patent system as an incentive to invest in those efforts and attempts which go by the name of research.” *In re Tomlinson* 363 F.2d 928, 931 (CCPA 1966).

Under the Examiner’s theory, conducting experiments with the possibility of success renders inventions obvious, if the experiment is actually successful; however, no court has applied this standard. By asserting that the present invention would be successful in light of the combined references, the Examiner has used impermissible hindsight.

In view of these remarks, Applicants respectfully submit that the cited references do not teach or even suggest, alone or in combination, the claimed invention. As such, this rejection of the claims should be withdrawn.

#### New Claims Presented

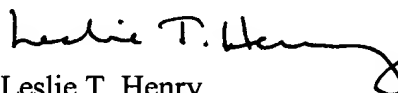
New claims 51-62 are directed to specific embodiments of the independent claims, where the subject being treated has breast cancer (claims 51, 54, 57, and 60), the anti-HER2 antibody is a humanized form of the murine antibody 4D5 or 520C9 (claims 52, 55, 58, and 61), and the IL-2 is recombinantly produced human IL-2 or biologically active variant thereof (claims 53, 56, 59, and 62). Applicants respectfully submit that the specification provides sufficient written description for the newly claimed subject matter and that this claimed subject matter is fully enabled by the specification. In addition, Applicants submit that the newly claimed subject matter is not taught or suggested by the cited references for reasons noted above. Accordingly, the rejections under 35 U.S.C. §§112, first paragraph, 102(b), and 103(a) should not be applied to the newly submitted claims.

### CONCLUSION

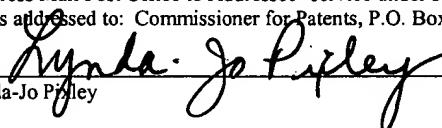
In view of the aforementioned amendments and remarks, Applicants respectfully submit that the objections to the specification, and the rejections of the claims under 35 U.S.C. §§112, first paragraph, 102(b), and 103(a) are overcome. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR §1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



Leslie T. Henry  
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<b>CUSTOMER NO. 00826</b> <b>ALSTON &amp; BIRD LLP</b> Bank of America Plaza 101 South Tryon Street, Suite 4000 Charlotte, NC 28280-4000 Tel Raleigh Office (919) 862-2200 Fax Raleigh Office (919) 862-2260	<p>"Express Mail" mailing label number EV 184330196 US Date of Deposit September 15, 2003</p> <p>I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p>  Lynda-Jo Pixley
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